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Review

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The cognitive functions of the cerebellum and its role in neurodegenerative diseases

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Abstract

The cerebellum has long been associated with motor control. However, its role in cognitive functions has attracted increasing attention recently. The uniformity of cerebellar internal structure seems at odds with its involvement in such diverse cognitive functions. Nonetheless, in cerebellar diseases such as ataxia, there is a comorbidity of motor and cognitive impairments, raising essential questions about how and to what extent the cerebellum participates in cognitive functions. This review begins by tracing the historical development of cerebellar research, suggesting that the diverse connections between the cerebellum and cerebral cortex, basal ganglia, and other subcortical nuclei form the basis for the cerebellum's role in regulating cognitive functions. We then delve into its involvement in language, reward-based learning, working memory, and spatial cognition. Additionally, we summarize the changes in the cerebellum observed in Alzheimer's disease (AD), Parkinson's disease (PD), and ataxias and their impact on cognitive functions. By discussing the role and mechanism of the cerebellum in cognition in physiology and pathology from the aspects of structure and function, we aim to shed light on promising new therapeutic targets related to the cerebellum for cognitive impairment.

Keywords: Cerebellum, cognition, Alzheimer's disease, Parkinson's disease, ataxia

INTRODUCTION

The earliest study of the cerebellum was authored by Vincenzo Malacarne in 1776 when he was investigating the relationship between the size of the human cerebellum and intelligence, in which he described many structures of the cerebellum, such as vermis, tonsil, nodulus, and lingula[1]. Approximately half a century later, Jean Marie Pierre Flourens demonstrated through experiments on pigeons that damage to the cerebellum led to a decline in their ability to fly, and such decline was not due to a loss of muscle strength, but instead to a loss of the coordination of their voluntary wing movements[2]. Subsequently, a series of research studies conducted on cerebellum lesioned monkeys[3-5], along with clinical observations of patients with cerebellar injuries[6-11], reported that cerebellum syndrome was characterized by ataxic motor symptoms (e.g., incoordination of balance, gait, extremity, and eye movements) and vestibulo-cerebellar syndrome (e.g., imbalance, nystagmus, and vertigo). On the other hand, the cognitive and psychiatric symptoms resulting from the cerebellar lesions tend to be subtle, diverse, and less immediately apparent compared to overt motor deficits. This is probably why the cerebellum has been regarded as a center devoted solely to motor control (including vestibular and oculomotor) for nearly 200 years, overlooking its role in cognitive functions since then. It was not until the late 1980s and early 1990s that the cognitive functions of the cerebellum began to be explored, initiated by Schmahmann's groundbreaking series of studies on patients with cerebellar lesions[12]. They conducted a clinical study of 20 patients with diseases confined to the cerebellum and found that those with lesions in the posterior lobe and vermis of the cerebellum exhibited the most significant clinical behavioral changes. These changes were characterized by impairments in executive functions, difficulties with spatial cognition, personality changes, and language deficits[13]. This newly defined clinical entity was termed the "cerebellar cognitive affective syndrome (CCAS)", now also known as Schmahmann syndrome. Furthermore, with the establishment and development of theoretical models such as the universal cerebellar transform (UCT)[12,14-16], which proposes that the cerebellum performs a consistent type of information processing across its motor and non-motor functional domains, alongside additional anatomical evidence[17-20], attention has gradually shifted toward the cerebellum's non-motor functions and the concept boundary of cerebellum syndrome has also been expanded. It is now well-known that CCAS has become the third cornerstone of clinical ataxiology[21], alongside the cerebellar motor syndrome and the vestibulo-cerebellar syndrome, caused by lesions in the cerebellar motor and vestibular regions, respectively.

In recent years, the role of the cerebellum in cognition has received increasing attention, leading to more in-depth research. Functional magnetic resonance imaging (fMRI) studies conducted on healthy humans have demonstrated that the cerebellum is involved in higher-order cognitive functions, including language function, reward and learning, working memory, and spatial cognition[22,23]. Additionally, as the role of cerebellum in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) gains increasing attention[24-26], along with the rising number of cognitive impairments observed in these conditions[27-29], there is also a growing focus on cerebellum's contribution to the cognitive deficits in these diseases.

This review outlines the current research on the cerebellum's involvement in cognition. We summarize evidence of the anatomical and neural circuits involved in cerebellar-related cognitive functions, the role of the cerebellum in various cognitive functions, and the cognitive impairments resulting from cerebellar lesions in the context of neurodegenerative diseases such as AD, PD, and ataxias, to help readers further understand the connection between the cerebellum and related cognitive functions, inspiring deeper exploration into the role of the cerebellum in cognition. Additionally, we include the changes in the cerebellum in relevant neurodegenerative diseases and their impact on cognitive impairments within these diseases, thereby implying that the cerebellum may be a potential therapeutic target for these conditions.

ANATOMICAL AND NEURAL CIRCUIT SUBSTRATES

Unlike the cerebral cortex, the neural circuits within the cerebellum exhibit a high degree of uniformity. Ramón y Cajal (1909) was the first to give a detailed description of the three-layer structure of the cerebellar cortex, identifying molecular layer, Purkinje cell layer, and granular cell layer. Climbing fibers transmit information from the olivary complex, while mossy fibers originate from various afferent sources. Ultimately, these inputs converge onto the Purkinje cells, which then relay the signals to the three deep cerebellar nuclei, the fastigial, interposed, and dentate nucleus, constituting the primary output of the cerebellum. Such a kind of modular circuity, including some inhibitory interneurons, remains largely fixed within the anatomical structure of the cerebellum[30]. Unipolar brush cells, the only excitatory interneurons in the cerebellum, may introduce some heterogeneity into internal neural circuity, but they are found only in the vestibulocerebellum[31].

From the perspective of its functions, the cerebellum can be broadly divided into two subregions: motor cerebellum and cognitive cerebellum. The motor cerebellum is primarily located in the anterior part of the cerebellum, including lobules V, VI, and VIII, while the cognitive cerebellum is situated in the posterior part, including crus I and II [Figure 1A]. Patients with cerebellar damage confined to the posterior part exhibited primarily cognitive dysfunctions, e.g., acute psychomotor retardation, infrequent speech, and mild cognitive decline, while their motor functions were largely unaffected[32,33]. In fMRI studies on healthy subjects, the activation patterns of the cerebellum were consistent with its anterior-posterior functional organization; during movement, there was significant activation in the anterior lobe and lobule VIII of the cerebellum, whereas cognitive tasks primarily activated the posterior and lateral regions of the cerebellum[34,35]. These anatomical locations correspond with the functional findings observed in patients with cerebellar lesions.

The functional differences in distinct cerebellar regions are closely related to their connections with external brain regions, such as the cerebral cortex, basal ganglia, and other subcortical regions[18,36]. In contrast to the repeated canonical circuit architecture within the cerebellum, the afferent and efferent connections of the cerebellum exhibit significant heterogeneity and are characterized by high functional specificity.

Connections between cerebellum and cerebral cortex

The cortico-ponto-cerebellar and the cerebello-thalamo-cortical circuitry are the two main pathways connecting the cerebellum with the cerebral cortex [Figure 1B]. Feedforward information is transmitted from the cerebral cortex to the cerebellum through the former circuit, and the cerebellum then processes this information and provides feedback to the cerebral cortex. Using trans-synaptic tracing techniques, projections from the arm region of the primary motor cortex (M1) to lobules IV-VI of the cerebellar cortex have been identified, as well as projections from area 46 of the dorsolateral prefrontal cortex (PFC) to crus II and lobule X, indicating feedforward projections[37]. Furthermore, within the cerebellar nuclei, the dorsal part of the dentate nucleus and interposed nucleus project to M1, while the ventral part of the dentate nucleus projects to area 46[19,38], indicating feedback projections.

The conventional view suggests that the cerebellum connects with the motor cortex through the cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways, participating in sensorimotor coordination. However, these parallel sub-circuits are widely present in the cerebrum and cerebellum and precisely connect different areas of the cerebral cortex with corresponding regions of the cerebellum, serving essential functions in various tasks. Anatomical studies have demonstrated that the cognitive-related cortical areas, such as the PFC, can also project to the cerebellum through cerebello-thalamo-cortical pathways, while the cerebellum reciprocally projects back to these brain regions via cortico-ponto-cerebellar pathways as

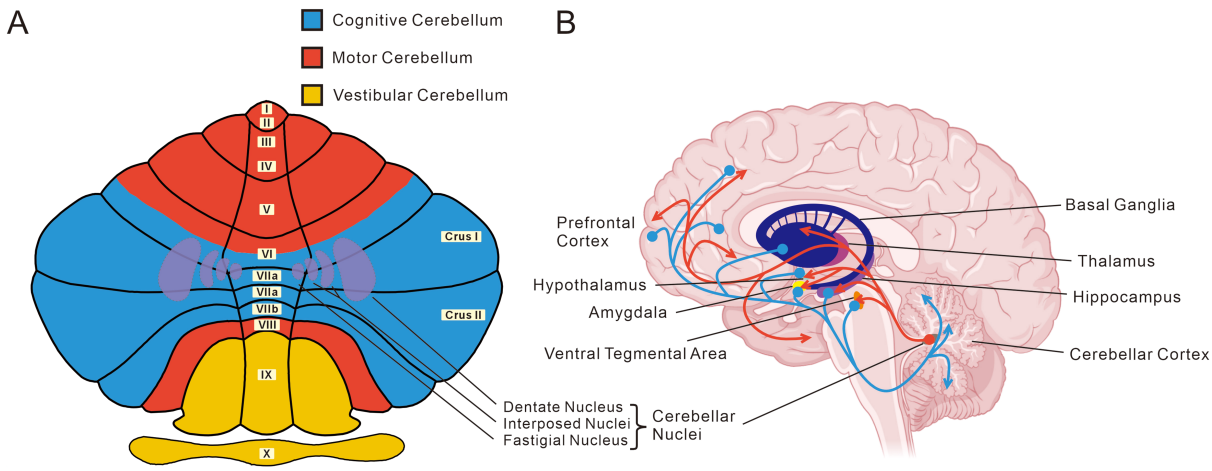

Figure 1. The anatomical and neural circuit basis of cerebellar involvement in cognitive functions. (A) An illustration of an unfolded cerebellum showing its ten lobules, depicting the topological structures of the motor, cognitive, and vestibular cerebellum. Notably, the anterior part of lobule VI is associated with the motor cerebellum, while the posterior part is linked to the cognitive cerebellum; (B) The connections related to cognition between the cerebellum and the cerebral cortex, basal ganglia, and other cognition-related subcortical brain regions.

well[39,40]. These connections have also been confirmed by functional connectivity observed in fMRI studies[41,42], suggesting that the cerebellum is involved in cognitive functions through its interactions with the cerebral cortex.

Connections between cerebellum and basal ganglia

The cerebellum and basal ganglia are widely regarded as two major subcortical motor structures. These two brain regions are extensively connected to the cerebral cortex through separate circuits[43]. It had been believed that the cerebellum and the basal ganglia were anatomically distinct subcortical systems that performed unique functional operations, and connections between these two regions occurred mainly at the level of the cerebral cortex[44,45]. However, anatomical connections between the cerebellum and basal ganglia have been explored and recognized during the past decade, with their functions extending beyond motor control[46-49] [Figure 1B].

In 2010, a study using retrograde transneuronal tracing techniques in *Cebus* monkeys revealed that the subthalamic nucleus sent a substantial disynaptic projection to the cerebellar cortex[46]. Two recent studies have confirmed that the subthalamic nucleus sends an afferent pathway that connects with the ipsilateral cerebellar cortex via the relay of pontine nuclei[47,48]. In addition, it has been reported that the efferent projection of the dentate nucleus passes through the thalamus and projects to the striatum and the external segment of the globus pallidus[47,48]. Furthermore, there is evidence of a direct circuit linking the dentate nucleus to the internal globus pallidus and substantia nigra based on a constrained spherical deconvolution tractography study carried out on humans[49]. Previous research has demonstrated a concurrent activation of the cerebellum and basal ganglia during reward-related learning[50,51], suggesting that these pathways may be involved in the cognitive processes underlying reward and learning. Moreover, Silveri noted that the circuit connections between the cerebellum and basal ganglia played a crucial role in language production[52], underscoring the diverse functions of cerebellar-basal ganglia pathways in various cognitive processes.

Connections between the cerebellum and other subcortical regions

Carta *et al.* reported in mice that the cerebellar nuclei directly project to the ventral tegmental area (VTA), a brain region crucial for processing and encoding reward[53]. It has been proved that the projection from the

cerebellum to VTA is necessary for social preference in mice, and the cerebellar inputs to VTA inputs are rewarding[53]. Furthermore, optogenetic activation of this projection enhances social behaviors[53]. These findings indicate cerebellar inputs to VTA modulate the reward pathway and play a prominent role in social behavior [Figure 1B].

The hippocampus is a critical brain region for spatial memory and navigation, and it also has circuit connections with the cerebellum, involved in spatial cognition. Using retrograde transneuronal tracing techniques in mice, it has been discovered that the cerebellum is connected to the dorsal hippocampus via intermediary neurons[54]. A constrained spherical deconvolution analysis of humans also revealed the connection between the cerebellum and hippocampus[55], consistent with the findings observed in mice. A resting-state fMRI study in the human brain also indicated that abnormal changes in functional connectivity between the cerebellum and the left hippocampus, as well as between the cerebellum and the right cingulate gyrus, contribute to a range of cognitive impairments resulting from cerebellar infarction[56]. These anatomical and functional findings suggest that the connections between the cerebellum and the hippocampus play a significant role in cognition [Figure 1B].

Hypothalamus, an integral component in the limbic system, plays a pivotal role in stress responses and emotional regulation, primarily through pathways such as the hypothalamic-pituitary-adrenal (HPA) axis[57]. Studies have revealed intricate connections between the hypothalamus and the cerebellum. Our previous studies have suggested that the hypothalamus can modulate cerebellar neuronal activity through histamine and orexin, thereby influencing cerebellar motor control and participating in somatic and non-somatic integration[58-62]. Such histaminergic and orexinergic inputs are likely to be involved in not only basic somatic motor control but also higher cognitive and emotional functions[63,64] [Figure 1B].

The amygdala is a critical center of the limbic system, responsible for emotional processing and memory. Using fluorescence micro-optical sectioning tomography (fMOST) technology, we recently revealed a direct projection from the cerebellar dentate nucleus to the amygdala[62,65]. Clinical evidence shows that the severity of anxiety symptoms in patients with PD is inversely correlated with the activity of this circuit[62]. Animal studies indicate that this circuit can be activated by exercise and plays a crucial role in alleviating anxiety[62]. Notably, the amygdala has been recognized for its significant role in cognition, especially social cognition[66]. Whether the cerebello-amygdalar circuit contributes to cognitive functions still needs further investigation [Figure 1B].

ROLE OF CEREBELLUM IN COGNITION

The extensive connections between the cerebellum and cognition-related brain structures provide the anatomic basis for the involvement of the cerebellum in cognitive functions, including language function, reward and learning, working memory, and spatial cognition.

Cerebellum in language function

Complex language, a higher cognitive function unique to humans, involves the coordinated processing of multiple cortical and subcortical brain regions. Traditionally, it has been believed that language is primarily associated with Broca's area in the frontal cortex and Wernicke's area in the superior temporal cortex[67]. However, the role of the cerebellum in language processing is receiving increasing attention. As early as 1988, by using positron emission tomography (PET), a study measured regional changes in average blood flow during the processing of single auditory or visual words, and the cerebellum was found to be significantly activated in verb-for-noun generation paradigms[68]. Two fMRI studies in 2014 and 2017 are consistent with the findings. Increased activation in the right cerebellar lobule VII was observed during

sentence completion tasks, where participants predicted the most suitable word to complete a sentence based on its context[69,70]. A recent study in 2022 demonstrated that the connections between cerebellar lobule VI and the dorsal anterior cingulate cortex/pre-supplementary motor cortex might hold a key position in the language control network[71] [Table 1].

Moreover, cerebellar lesions can adversely affect a patient's language abilities. A study on a patient with neurogenic stuttering caused by brain infarction showed that preexisting thalamic hemorrhage or frontal lobe infarction did not lead to stuttering, while significant stuttering occurred after a cerebellar infarction[77]. A more in-depth study indicated that patients with cerebellar damage exhibited more metalinguistic deficits, while their grammatical and semantic abilities were relatively preserved[78]. This pattern of language impairment supports the dysmetria of thought theory, which posits that cerebellar cognitive deficits follow a logic like that of motor deficits: cerebellar damage disrupts the regulation of movement without impairing its generation (leading to dysmetria but not weakness), and similarly, it disrupts the regulation of language without impairing its generation (leading to metalinguistic deficits but not aphasia).

Another interesting phenomenon is the lateralization of cerebellar language functions, with a notable right-sided dominance. This may be due to the language centers in the left cerebral cortex, as the cerebellum is connected to the contralateral cerebral cortex[22,23]. Using anodal transcranial direct-current stimulation (tDCS) to modulate the right cerebellar crus I and II can alter the cerebellar signaling during predictive language processing and enhance functional connectivity within the reading/language network[70].

Cerebellum in reward and learning

The role of the cerebellum in reward and learning also attracts increasing attention. Using two-photon calcium imaging in behaving mice, a recent study showed that some cerebellar granule cells responded preferentially to reward or reward omission, whereas others selectively encoded reward anticipation[79]. Additionally, climbing fibers can not only directly respond to rewards[80-82] but also encode the magnitude of expected rewards[83,84]. This aligns with observations of cerebellar macro-activity. A meta-analysis of human brain fMRI studies demonstrated that reward anticipation was associated with regional activity in the bilateral anterior lobe, bilateral lobule VI, left Crus I, and the posterior vermis, while reward outcome was related to regional activity in the declive and left lobule VI[85]. These findings demonstrate the distinct involvement of the cerebellum in reward anticipation and outcome processing.

An experiment comparing patients with cerebellar ataxia to healthy controls showed that individuals with cerebellar ataxia had severely impaired reward learning from trial-and-error feedback but retained the ability to predict rewards based on contextual memory[86]. Their findings suggest that the cerebellum may play a special and necessary role in incremental learning based on reinforcement-reward associations. Additionally, this work proposes that the cerebellum collaborates with the basal ganglia to support reinforcement learning from rewards, extending beyond motor learning. A study on monkey's eye movements indicates that the cerebellum inputs reward expectation and movement signals into the basal ganglia, which processes this information and outputs information with a higher signal-to-noise ratio[72] [Table 1]. Furthermore, fMRI functional connectivity analysis shows that connectivity between the ventral striatum and the cerebellum increases during reward anticipation[73] [Table 1].

The underlying basis of these phenomena may be the plasticity changes within the cerebellum itself and its connections with other brain regions, which may facilitate learning and memory. Several studies have demonstrated that the intrinsic plasticity of Purkinje cells within the cerebellum is vital for the consolidation

Table 1. The circuit mechanism studies of the cerebellum in cognition

Authors	Year	Circuits	Methods	Subjects	Functions
Yuan *et al.*[71]	2013	Connections between cerebellar lobule VI and dorsal anterior cingulate cortex/pre-supplementary motor cortex	fMRI	Human	Language control
Larry *et al.*[72]	2024	Caudate-SNpr-cerebellar vermis (Purkinje cell) pathway	*In vivo* electrophysiology	Macaca Fascicularis monkeys	Reward expectation and movement
Carruzzo *et al.*[73]	2023	Connections between the cerebellum and ventral striatum	fMRI	Human	Reward anticipation
Carta *et al.*[53]	2023	Connections between cerebellar nuclei (glutamatergic neurons) and VTA	Anterograde tracing and optogenetic manipulation	Mice	Reward in social behavior
Li *et al.*[74]	2022	Connections between lobule VI and right cingulate cortex/bilateral superior frontal gyrus	fMRI	Human	Verbal working memory
Bezdicek *et al.*[75]	2021	Connections between cerebellar lobule I-V and DLPFC	fMRI	PD patients	Working memory
Sako *et al.*[76]	2021	Connections between cerebellar lobule VII and visuospatial-executive-domain-related/attention-domain-related networks	fMRI	PD patients	Visuospatial execution and attention

fMRI: Functional magnetic resonance imaging; VTA: ventral tegmental area; DLPFC: dorsolateral prefrontal cortex; PD: Parkinson's disease.

of motor memory, and memory consolidation deficits ensue when the intrinsic plasticity is impaired[87,88]. Additionally, a single-cell RNA sequencing study revealed that Purkinje cells might be classified into two primary subgroups: Plcb4+ and Aldoc+, the former of which exhibited significant plasticity and played a crucial role in associative learning[89]. A fMRI study comparing young and older subjects also showed that associative learning altered the intrinsic functional connectivity strength within several cerebellar networks, e.g., frontal-cerebellar, temporal-cerebellar, and cerebello-cerebellar in younger subjects, with significantly lesser effects in older individuals. It suggests that the neural plasticity within these cerebellar networks may play a crucial role in associative learning[90].

The VTA and substantia nigra are two primary sources of dopamine, a neurotransmitter closely associated with reward learning, and are widely recognized for their roles in encoding and predicting rewards[91,92]. Recent anatomical studies have shown that the cerebellum sends extensive projections to both the VTA and substantia nigra[49,53] [Table 1]. A review focused on these cerebellar projections suggested that cerebellar connections to the VTA may influence reward-based learning, while the projections to the substantia nigra pars compacta (SNc) may contribute to motor vigor[93]. Additionally, it has been confirmed that the cerebellum receives dopaminergic innervation, with dopamine D1, D2, and D3 receptors detected within the cerebellum[94,95].

Cerebellum in working memory

Working memory, a cognitive system responsible for temporarily holding and manipulating information, relies heavily on the coordinated activity of several brain regions. The PFC, parietal lobe, and hippocampus are well-established contributors. With its extensive projections to these regions[48,93,94], the cerebellum is suggested to play a potential role in neural circuits related to working memory. A comprehensive study examining various pediatric cerebellar disorders - including tumors, cerebellar infarctions, congenital cerebellar malformations, and cerebellar abnormalities due to genetic or developmental causes - found that regardless of the etiology of cerebellar damage, patients consistently exhibited working memory impairments[96]. The detrimental impact of cerebellar damage on working memory persists into adulthood, maintaining the same impairments observed in earlier stages of life[97-99].

Recent studies combining working memory tasks and advanced technologies in healthy subjects have confirmed the cerebellum's involvement in working memory. A structural MRI study demonstrated that larger volumes of cerebellar crus I and the entire cerebellum correlate with better performance on a 2-back visual working memory task[100]. A functional MRI study revealed that cerebellar lobule VIIb/VIIIa selectively responds to memorized stimuli, indicating its role in storing and retrieving visual information[101]. Resting-state functional connectivity analyses showed that the strength of cortico-cerebellar circuit connections is associated with performances in working memory tasks[74] [Table 1].

Studies manipulating the cerebellum through transcranial magnetic stimulation (TMS) have further elucidated its role in working memory. One study demonstrated that applying 5 and 20 Hz repetitive TMS to the cerebellar crus II region in healthy subjects enhanced prefrontal excitability and significantly improved brain network efficiency, resulting in superior performance on working memory tasks compared to a sham stimulation group[102]. However, another TMS experiment targeting the left superior and left inferior cerebellum demonstrated that stimulation of these regions led to decreased accuracy on visual working memory tasks. Although different TMS parameters affect the cerebellum's influence on working memory tasks differently, these findings collectively highlight the critical role of the cerebellum in working memory processes[103].

Cerebellum in spatial cognition

Spatial cognition is an essential aspect of cognitive functions. Many studies have reported decreased spatial cognition in patients with bilateral cerebellar damage. These patients exhibit visuospatial organization disorders, have difficulties in planning daily activities[104], and even show deficits in spatial procedural learning[105,106]. Additionally, spatial learning impairments have been observed in mice with cerebellar mutation or rats with hemicerebellectomy[107].

Direct damage to the cerebellar nuclei also has various effects on spatial cognition. For instance, bilateral electrical lesions of the dentate nucleus in rats led to impaired learning in the hidden platform task of the Morris water maze. However, these lesions did not affect long-term retention, the probe trial, or the visuomotor guidance necessary for navigating toward a visible goal[108,109]. This selective impairment indicates the specific role of the dentate nucleus in spatial localization. In contrast, another study applied muscimol to completely inactivate all deep cerebellar nuclei, resulting in memory loss during the water maze task. Interestingly, this effect was not observed when the dentate nucleus was selectively inactivated, indicating that the fastigial nucleus and interposed nuclei are also critical regions for spatial cognition and may play a vital role in spatial memory[110].

The above evidence provides fundamental support for the involvement of the cerebellum in spatial cognition. However, the specific role it plays, and the types of neural signals it receives, integrates, and transmits, remain unclear. In addition, although the neural circuit connections between the cerebellum and hippocampus, the central structure for spatial memory and navigation, have been dissected, the role of these connections in spatial cognition remains unclear and requires further investigation.

CEREBELLUM AND COGNITIVE IMPAIRMENTS IN DISEASES

In this section, we will focus on the pathological changes of cerebellum in AD, PD, and ataxias, and explore the relationship between these changes and the associated cognitive impairments. Moreover, the impact of neuromodulation targeting the cerebellum on treating cognitive impairments in these diseases will be discussed.

Cerebellum and cognitive impairments in AD

AD is the most prevalent neurodegenerative disease worldwide. In 2015, approximately 29.8 million people globally were affected by AD[111], and the number of AD patients is expected to exceed 100 million by 2050[112]. The primary symptom of AD is dementia, which is often characterized by cognitive impairments such as memory loss, decline in spatial navigation abilities, and deterioration of language skills. AD has traditionally been associated with neurodegeneration in various cortical and subcortical brain regions, such as the hippocampus. However, accumulating evidence suggests that the cerebellum also undergoes age-related degenerative changes. A stereological study demonstrated that with aging, the total cortical volume of the cerebellum decreases by 10.8% over the lifespan, while its total volume declines by 25.9%, with various subregions experiencing different degrees of loss[113]. Accumulating studies show that cerebellar degeneration is also involved in the progression of AD.

At the molecular level, the cerebellar nuclei in AD patients also exhibit characteristic symptoms of AD-related cellular atrophy, such as ectopic cell cycle events and increased DNA damage. However, these alterations are primarily observed in the late stages of AD[114]. A voxel-based morphometry study revealed localized atrophy in the bilateral crus I and crus II regions of the cerebellum in AD patients, with the cerebellar regions showing atrophy also displaying stronger intrinsic functional connectivity with severely atrophic regions of the cerebrum. This suggests that cerebellar-cerebral circuit dysfunction may play a role in the pathogenesis of AD. Additionally, another study utilizing fluorodeoxyglucose-positron emission tomography (FDG-PET) scanned 830 AD patients and observed that a significant portion exhibited crossed cerebellar diaschisis (CCD), characterized by markedly reduced metabolic activity in the left temporal and occipital regions, as well as in the right cerebellum[115]. This further supports the notion of circuit dysfunction between the cerebral cortex and the cerebellum in AD patients. Moreover, a recent review indicated that degeneration of the inferior olivary nucleus in AD led to reduced input to the cerebellum, impairing its neuromodulatory functions, which may contribute to spatial navigation issues observed in the early stages of dementia[116]. A study involving 27 patients with AD also demonstrated that repetitive TMS (rTMS) targeting the bilateral cerebellum crus II significantly improved multi-domain cognitive functions, including overall cognitive levels, episodic memory, executive function, verbal ability, and visuospatial function[117]. These findings underscore the involvement of the cerebellum in AD and its significant role in the related symptoms.

Interestingly, the cerebellum appears to be relatively spared in the early stages of AD, leading some to speculate that the cerebellum may also play a compensatory role in the early cognitive deficits associated with AD[118], which is a hypothesis that warrants further investigation.

Cerebellum and cognitive impairments in PD

PD is the second most prevalent neurodegenerative disease in the world, following AD. People often focus more on the motor symptoms of PD, such as tremors, rigidity, postural instability, and akinesia, which are typically associated with dopaminergic neuron degeneration in the basal ganglia[24,25,119]. However, increasing evidence suggests that the cerebellum plays an important role in the motor symptoms seen in PD. As research progresses, there is growing attention to the cognitive impairments in PD and their association with the cerebellum[25].

At the molecular level, PD patients' cerebellum exhibits α-synuclein aggregation and Lewy body formation and deposition[120,121], which are key molecular markers of neuronal degeneration in PD. A study on emotional vocal encoding indicated that PD patients with deficits in recognizing emotional vocals showed more severe lesions in the right hemisphere of the cerebellum[122]. Functional MRI connectivity studies demonstrated that PD patients with mild cognitive impairment exhibited disrupted resting-state functional

connectivity between the bilateral dorsolateral prefrontal cortex (DLPFC) and the cerebellum, compared to PD patients with normal cognition. Furthermore, the weaker the functional connectivity between the DLPFC and the cerebellum, the poorer the performance on various working memory tasks[75] [Table 1]. In addition, a brain network study in PD patients identified the cerebellar lobule VII as a crucial node in visuospatial-executive-domain-related and attention-domain-related networks [Table 1].

Studies mentioned above indicate changes in the connectivity between the cerebellum and other brain regions in cognitive impairments associated with PD, while the cerebellum itself shows abnormally increased activity in PD. A PET study revealed that hypermetabolism in the anterior lobe and the vermis of the cerebellum correlated with the severity of motor dysfunction, while increased metabolic activity in the right crus I and crus II correlated with cognitive dysfunction[123]. Moreover, a neuroimaging meta-analysis indicated that PD patients with social perception impairments exhibited increased activation in the posterior cerebellum[124]. This increased neural activity in the cerebellum may play a compensatory role.

Neuromodulation targeting the cerebellum can also improve cognitive impairment in PD [Table 2]. In an open study[143], thirty patients with PD were stimulated with 1 Hz rTMS every half year for 1.5 years. After that, the tDCS was added to the stimulation over both sides of the cerebellum for the next 2 years. It was revealed that rTMS and tDCS improved the executive function of patients over 65 years. Given that cerebellar neuromodulation can also improve motor symptoms in PD [Table 2], the cerebellum emerges as a highly promising therapeutic target for ameliorating PD symptoms as well.

Cerebellum and cognitive impairments in ataxias

As previously mentioned, the cerebellum is traditionally associated with motor control. Consequently, cerebellar lesions often lead to noticeable motor impairments, with ataxias being the most characteristic condition, marked primarily by uncoordinated voluntary movements. Interestingly, ataxias, including pure spinocerebellar ataxia (SCA) and Friedreich ataxia (FRDA), are comorbid with cognitive impairments, highlighting the comorbidity of motor and cognitive impairments in cerebellar disorders.

A clinical study involving 35 SCA type 2 (SCA2) patients noted that 71.4% had cognitive impairments, including deficits in visuomotor construction, focused attention, learning and memory, language and fluency, and executive function[155]. Another psychometric evaluation revealed that SCA2 patients had lower general intelligence, executive function, and short-term and long-term verbal and visuospatial memory compared to age- and gender-matched healthy controls[156]. A review of SCA type 3 (SCA3) highlighted cognitive dysfunction, with multiple studies showing impairments, particularly in executive function[157]. Additionally, Orsi *et al.* identified memory, language, visuospatial, attention, executive, and emotional impairments across all gene-defined SCA categories[158].

Furthermore, a meta-analysis focusing on FRDA showed that individuals with FRDA performed significantly worse on most tasks related to language, attention, executive function, memory, visuospatial function, emotional regulation, and social cognition than those without FRDA. The degree of change in these cognitive functions was also correlated with cerebellar-related structural parameters, further indicating the cerebellum's role in the pathophysiology of cognitive impairment in FRDA[159]. Several reviews on cerebellar ataxias have pointed out that patients with cerebellar ataxias endure numerous cognitive impairments, emotional issues, and some neuropsychiatric symptoms[160-162].

Studies utilizing tDCS have demonstrated that neuromodulation of the cerebellum improves cognitive dysfunction associated with ataxias [Table 2], and after anodal cerebellar tDCS and cathodal spinal tDCS,

Table 2. Neuromodulation studies targeting the cerebellum in the last fifteen years

Authors	Year	Method	Target	Disease	Efficacy	Improvement of cognition
Grimaldi *et al.*[125]	2013	tDCS	Cerebellum (anode) and contralateral supra-orbital area (cathode)	Ataxia	Decreasing the amplitudes of long-latency stretch reflexes	
Grimaldi *et al.*[126]	2014	tDCS	Cerebellum and contralateral motor cortex (both anode)	Ataxia (SCA2)	Improving voluntary movements of the upper limbs	
Benussi *et al.*[127]	2015	tDCS	Cerebellum (anode) and right deltoid (cathode)	Ataxia	Improving posture, gait, and limb coordination	
Benussi *et al.*[128]	2017	tDCS	Cerebellum (anode) and right deltoid (cathode)	Ataxia	Improving all ataxic symptoms	
Bodranghien *et al.*[129]	2017	tDCS	Right cerebellar hemisphere (anode) and left motor cortex (cathode)	Ataxia (ARCA3)	Improving postural tremor	
Grecco *et al.*[130]	2017	tDCS	Cerebellum (anode) and central supraorbital region (cathode)	Ataxia caused by cerebral palsy	Improving balance combined with treadmill training	
Benussi *et al.*[131]	2018	tDCS	Cerebellum (anode) and spine (cathode)	Ataxia	Improving all ataxic symptoms	
Benussi *et al.*[132]	2021	tDCS	Cerebellum (anode) and spine (cathode)	Ataxia	Improving motor and cognitive symptoms	√
Naeije *et al.*[133]	2023	tDCS	Cerebellum (anode) and right deltoid (cathode)	Ataxia (Friedreich's ataxia)	Reducing motor and cognitive symptoms	√
Farzan *et al.*[134]	2013	TMS (rTMS)	Cerebellum	Ataxia	Improving limb coordination, speech, and gait	
Bonnì *et al.*[135]	2014	TMS (iTBS)	Lateral cerebellum	Ataxia caused by cerebellar stroke	Improving ataxic gait and posture symptoms	
Kim *et al.*[136]	2014	TMS (rTMS)	Cerebellar hemisphere ipsilateral to the ataxic side	Ataxia caused by acute posterior circulation stroke	Improving walking and balance	
Cury *et al.*[137]	2015	TMS (rTMS)	Healthy dentate nucleus	Ataxia caused by unilateral cerebellar infarction	Improving tremor and cerebellar ataxia	
Dang *et al.*[138]	2019	TMS (rTMS)	Cerebellum	Ataxia (SCA6)	Improving motor and speech function	
França *et al.*[139]	2020	TMS	Cerebellum contralateral to the most clinically affected side	Ataxia	Improving ataxic symptoms	
Teixeira *et al.*[140]	2015	DBS	Healthy dentate nucleus	Ataxia caused by cerebellar stroke	Improving tremor and cerebellar ataxia	
Miterko *et al.*[141]	2021	DBS	Bilateral interposed cerebellar nuclei	Ataxia in Car8^{wdl} mice	Improving motor behaviors of Car8^{wdl} mice	
Ferrucci *et al.*[142]	2016	tDCS	Cerebellum and M1 (anode) and right deltoid (cathode)	PD	Improving levodopa-induced dyskinesias	
Málly *et al.*[143]	2018	rTMS and tDCS	Hemispheres of the cerebellum (anode) and middle part of the frontal area (cathode) for tDCS, and DLPFC and brainstem for rTMS	PD	Slowing the progression of PD in an age-dependent way	√
Workman *et al.*[144]	2020	tDCS	Cerebellar hemisphere contralateral to the more PD-affected side(anode) and contralateral upper arm or cerebellar hemisphere ipsilateral to the more PD-affected side (cathode)	PD	Improving balance performance	

Koch *et al.*[145]	2009	TMS (cTBS)	Lateral cerebellum	PD	Decreasing levodopa-induced dyskinesias	
Minks *et al.*[146]	2011	TMS (rTMS)	Right lateral cerebellum	PD	Improving gross motor skills and worsening fine motor skills	
Brusa *et al.*[147]	2012	TMS (cTBS)	Lateral cerebellum	PD	Reducing levodopa-induced dyskinesia	
Bologna *et al.*[148]	2015	TMS (cTBS)	Ipsilateral cerebellar hemisphere	PD	No influence on the generation of resting tremor in PD	
Di Biasio *et al.*[149]	2015	TMS (cTBS)	Cerebellar hemisphere ipsilateral to the more affected side	PD	Improving STDT exclusively when patients were OFF therapy	
Lefaivre *et al.*[150]	2016	TMS (rTMS)	Cerebellar vermis or lateral cerebellum	PD	Improving resting tremor (lateral cerebellum was better)	
Di Lorenzo *et al.*[151]	2013	TMS (cTBS)	Posterior and superior lobules of the lateral cerebellum	AD	Affecting SLAI	
Yao *et al.*[117]	2022	TMS (rTMS)	Bilateral cerebellum crus II	AD	Improving multi-domain cognitive functions	√
Demirtas-Tatlidede *ei al.*[152]	2010	TMS (iTBS)	Cerebellar vermis	Schizophrenia	Improving negative symptoms, mood, and cognition	√
Minichino *et al.*[153]	2015	tDCS	PFC (anode) and cerebellum (cathode)	Bipolar disorder	Improving visuospatial memory, executive function, and motor coordination	√
Sebastian *et al.*[154]	2016	tDCS	Cerebellum (anode) and right deltoid (cathode)	Aphasia	Augment spelling therapy	√

OFF refers to a change in the clinical state of a PD patient where motor and/or non-motor symptoms appear or worsen and result in functional disability. tDCS: Transcranial direct-current stimulation; SCA2: spinocerebellar ataxia type 2; ARCA3: autosomal recessive cerebellar ataxia type 3; TMS: transcranial magnetic stimulation; rTMS: repetitive transcranial magnetic stimulation; iTBS: intermittent theta burst stimulation; SCA6: spinocerebellar ataxia type 6; DBS: deep brain stimulation; PD: Parkinson's disease; DLPFC: dorsolateral prefrontal cortex; cTBS: continuous theta burst stimulation; STDT: somatosensory temporal discrimination threshold; AD: Alzheimer's disease; SLAI: short-latency afferent inhibition; PFC: prefrontal cortex.

patients with cerebellar ataxias showed significant improvements in motor scores, cognitive function, and quality of life[132]. Additionally, a week of anodal cerebellar transcranial direct current stimulation (ctDCS) treatment alleviated both motor and cognitive symptoms in FRDA patients[133]. Interestingly, numerous studies have shown that cerebellar-targeted neuromodulation improves motor symptoms in ataxias [Table 2]. This suggests that the cerebellum may serve as a common target for treating both motor and cognitive impairments, highlighting its significant therapeutic potential in ataxias.

In summary, AD and PD patients with cognitive impairments show neurodegeneration in the cerebellum, and cerebellar ataxias are often accompanied by cognitive deficits. Therefore, cerebellar neurodegeneration may be actively involved in the cognitive dysfunction of AD, PD, and ataxias. These findings indicate that neuromodulation targeting the cerebellum may be a potentially effective strategy for alleviating cognitive symptoms in these disorders.

CONCLUSION

The cerebellum has historically been recognized for its role in motor control and coordination, but it is now increasingly regarded as crucial for various cognitive functions. We elucidated the extensive neural connections between the cerebellum and external brain regions, including the cerebral cortex, basal ganglia, and other subcortical areas. Building on this anatomical and neural circuit foundation, we further demonstrated the crucial role of the cerebellum in various higher-order cognitive processes, such as language, reward-based learning, working memory, and spatial cognition. Finally, we explored the changes in the cerebellum in different diseases, including ataxia, PD, and AD, and their impact on cognitive functions, and proposed that the cerebellum could serve as a therapeutic target for treating cognitive impairments associated with these diseases.

However, many questions in this field remain unresolved. Although the establishment of the UCT theory provides a reasonable framework for understanding the role of the cerebellum in both motor and cognitive functions, the specific mechanisms of how the cerebellum's homogenous internal structure processes and outputs signals from different brain regions remain unclear. For example, at the molecular level, besides classical glutamatergic and GABAergic signals, diverse neurotransmitters and neuromodulators are present in the cerebellum, including amines like dopamine[79], norepinephrine[163], and histamine[60], and neuropeptides[164] like oxytocin[165], CRF[166], and orexin[167]. Their roles in processing motor and cognitive functions are still largely unknown. At the cellular level, single-cell sequencing has revealed the high heterogeneity of neurons in the cerebellum[89], but the roles of different cell clusters in cerebellar motor and cognitive control remain to be elucidated. Furthermore, it is essential to investigate the nature of the signals transmitted from the cerebellum to various brain regions, such as the cortex, basal ganglia, and amygdala, and how the cerebellum dynamically interacts with other brain areas to collectively perform a range of higher cognitive functions. In addition, from the perspective of pathophysiology, significant cerebellar deficits often occur in the late stage of AD and PD, suggesting that cerebellar dysfunction may arise as a secondary effect of widespread brain degeneration and network disruptions. However, considering the reciprocal connections between the cerebellum and cerebral cortex/basal ganglia, whether the cerebellum-mediated cognitive control holds a position in the early stage of AD and PD remains to be determined.

Lastly, as shown in Table 2, neuromodulation targeting the cerebellum in ataxias and PD predominantly focuses on improving motor functions, while neuromodulation for AD mainly targets DLPFC[168-179]. However, in certain psychiatric disorders, such as schizophrenia[152], bipolar disorder[153], and aphasia[154], cerebellar-targeted neuromodulation has been shown to improve related cognitive functions significantly. Although the precise targeting of specific cerebellar subregions or circuits for cognitive regulation still faces challenges, the potential of the cerebellum as a neuromodulation target for enhancing cognitive function in neurodegenerative diseases is likely underestimated and deserves more attention.

DECLARATIONS

Authors' contributions

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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